PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Stakeholder engagement in economic evaluation: Protocol for using the nominal group technique to elicit patient, healthcare provider, and health system stakeholder input in the development of an early economic evaluation model of chimeric antigen receptor T-cell therapy
AUTHORS	Wilson, Mackenzie; Thavorn, Kednapa; Hawrysh, Terry; Graham, Ian; Atkins, Harold; Kekre, Natasha; Coyle, Doug; Lalu, Manoj; Fergusson, Dean; Chan, Kelvin; Ollendorf, Daniel; Presseau, Justin

VERSION 1 – REVIEW

REVIEWER	Petrou, Panagiotis University of Nicosia, Department of Life and Heatlh Sciences
REVIEW RETURNED	16-Dec-2020

GENERAL COMMENTS	This is a tidy paper with prope structure. Nevertheless, i cannot see any value stemming out of enganging stakeholder in technical field, such as economic evaluation of CAR-T therapy.

REVIEWER	Heyman, Benjamin University of California San Diego, Medicine
REVIEW RETURNED	26-Jan-2021

GENERAL COMMENTS	The authors present a protocol and discussion for an upcoming study on the health and economic evaluation of CAR T cell therapy for patients with hematologic malignancies. They are employing an innovative approach to engage multiple stakeholders to answer important questions regarding economic evaluation of this treatment modality. It may be challenging to obtain all the necessary results and recruit the participants, but the investigators have a plan in place that appears to hopefully mitigate potential obstacles. I look forward to seeing the results of their work.

REVIEWER	Ijzerman, Maarten University of Twente
REVIEW RETURNED	12-Feb-2021

GENERAL COMMENTS	Dear authors, thank you for submitting this paper and for your efforts to engage with stakeholders in the development of health economic models. I appreciate the opportunity to review and wish to make a few high-level comments to further improve and clarify the work you intend to start.

	1. As you state in the introduction, stakeholder engagement in HTA is not new and is a constant focus for many HTA agencies. However, your paper is not about the role of stakeholders in HTA, but about their role in the development of health economic models, which is quite different. The reason for bringing this up is that you may need to emphasise the unique contribution of this paper a bit more, for instance by using a different title and be more clear about this in abstract and introduction. I'd also recommend to refer to the environmental literature and make a comparison and to elaborate why this may be important for health economic models (or may not work). 2. Definition of early Health Economic Model. It was not clear why the objective is to develop an early or iterative model (not necessarily the same). It would be helpful to define more carefully what decision the early model is expected to inform. If it is iterative, ie is the expectation to inform decisions along the development of the model or with more evidence becoming available? 3. Exploring experiences in public policy I had the privilege to work with public policy scientists on a few papers and there is some interesting literature in that space you may need to refer to. This is not only limited to stakeholders perspectives on developing the models, but also about stakeholders perspectives relevant to make an impact in policy. 4. Defining stakeholders and decision makers Most of the models we develop in HTA have a rather limited scope compared to some of the environmental models you refer to in the literature. The decision is relevant for a (very) small group of patients and the decision makers involved are relatively limited. Potentially, there is a much larger group of stakeholders either directly or indirectly using the evidence presented in the models. For instance, neither industry reps nor politicians are included. I can see why not, but they can be dominant and clearly play a role in use of economic evaluation results. I'd recommend to carefully define stakeholder groups, to define their potential role and dominance in the use of economic evaluation results. 5. Alignment with guidelines Many of the health economic models are developed based on modelling guidelines issued by HTA agencies. These guidelines prescribe what evidence needs to be demonstrated and what the base case should be. Can the authors please indicate how much opportunity there is to deviate from these guidelines by consulting with stakeholders? Or, alternatively, how can we ensure that stakeholder perspectives are given a weight in the model development by users of these models. 6. Methods used I have insufficient experience with the NGT methods used, but there are similarities with MCDA methods. Three questions with regard to the proposed methods, (1) why define separate stakeholder groups and why don't you bring them together to discuss different perspectives (see decision conferencing methods), (2) the exploration and structuring phase can all be brought into one session, is this considered? and (3) you refer to ranking but no

	methods are defined. How obtained and are these ranks used to facilitate the group discussion?

VERSION 1 – AUTHOR RESPONSE

REVIEWER REPORTS

Reviewer: 1

Dr. Panagiotis Petrou, University of Nicosia

Comments to the Author:

This is a tidy paper with prope structure. Nevertheless, i cannot see any value stemming out of enganging stakeholder in technical field, such as economic evaluation of CAR-T therapy.

Thank you for taking the time to review our manuscript and for providing your feedback.

Patient and public involvement in research represents an important advancement that has been recognised across several research disciplines and technical fields, such as clinical trials and economic evaluation. Involving key stakeholders in this research ensures that their perspectives are reflected in the evaluation, its associated outputs, and its subsequent contribution to healthcare decision-making. Overall, this involvement may enhance the validity and generalizability of the early health economic evaluation model. In the instance of an early economic evaluation of a novel cancer therapy, such as CAR-T therapy, involving the individuals for whom the therapy is designed for aligns with the global push for person-centred care and is a moral imperative in this regar

Since the exploration of stakeholder engagement in the development of early health economic models represents a relatively new line of inquiry, we plan to assess different stakeholder groups' interest in being involved in such processes and report the influence of this engagement on the development of the health economic model. The outputs of this research are thus intended to inform whether there is an interest from stakeholders for this form of engagement, what future engagement might look like, and how this engagement might influence health economic models. This foundational understanding will provide insight into the value of stakeholders' contributions to health economic model development and inform future patient and public engagement in this field of research.

Reviewer: 2

Dr. Benjamin Heyman, University of California San Diego

Comments to the Author:

The authors present a protocol and discussion for an upcoming study on the health and economic evaluation of CAR T cell therapy for patients with hematologic malignancies. They are employing an innovative approach to engage multiple stakeholders to answer important questions regarding economic evaluation of this treatment modality. It may be challenging to obtain all the necessary results and recruit the participants, but the investigators have a plan in place that appears to hopefully mitigate potential obstacles. I look forward to seeing the results of their work.

Thank you for taking the time to review the manuscript and for your positive feedback. We likewise acknowledge the novelty and importance of including patient and healthcare stakeholders' perspectives in the development of early health economic evaluation models.

We acknowledge that we are likely to encounter challenges to recruitment given the technical nature of economic evaluation and the limited experience of key stakeholders, such as patients and healthcare stakeholders, in this area of work. Additionally, we expect that these challenges are likely to be exacerbated as a result of the global COVID-19 pandemic. We have adapted our methods for an online environment to accommodate limitations to in-person congregation for the duration of the pandemic. The research team remains flexible to adapt to the quickly evolving circumstances as a result of the pandemic to facilitate recruitment of the identified key stakeholder groups, and will report any deviations from the protocol in the results write up.

Reviewer: 3

Maarten Ijzerman, University of Twente

Comments to the Author:

Dear authors, thank you for submitting this paper and for your efforts to engage with stakeholders in the development of health economic models. I appreciate the opportunity to review and wish to make a few high-level comments to further improve and clarify the work you intend to start.

1. As you state in the introduction, stakeholder engagement in HTA is not new and is a constant focus for many HTA agencies. However, your paper is not about the role of stakeholders in HTA, but about their role in the development of health economic models, which is quite different. The reason for bringing this up is that you may need to emphasise the unique contribution of this paper

a bit more, for instance by using a different title and be more clear about this in abstract and introduction. I'd also recommend to refer to the environmental literature and make a comparison and to elaborate why this may be important for health economic models (or may not work).

Thank you for this comment and for highlighting the differentiation of this work from traditional stakeholder engagement in HTA literature and practice. We've updated the title to be more clear about the unique contribution of our manuscript (new text is underlined): 'Stakeholder engagement in economic evaluation: Protocol for using the nominal group technique to elicit patient, healthcare provider, and health system stakeholder input in the development of an early economic evaluation model of chimeric antigen receptor T-cell therapy'. To further clarify and emphasise this point, we've included additional details in the abstract and introduction; namely, the following text has been updated in the abstract (new text is underlined):

'Traditionally, stakeholders are engaged in certain parts of health technology assessment processes, such as in the identification and selection of technologies, formulation of recommendations, and implementation of recommendations; however, little is known about processes for stakeholder engagement during the conduct of the assessment. This is especially the case for economic evaluations. Stakeholders, such as ~~engagement in economic evaluations has included~~ clinicians, policy makers, ~~and reimbursement decision-makers; however, other stakeholders, such as~~ patients and their families, have insight into factors that can enhance the validity of an economic evaluation model. Involving all key stakeholders in the development of an early economic evaluation model of CAR-T cell therapy responds to a call in the literature for ~~this form of~~ greater stakeholder engagement. This research outlines a specific methodology for stakeholder engagement and represents an avenue to enhance health economic evaluations ~~evidence~~ and support the use of these models to inform ~~policy~~ decision-making for resource allocation. This protocol may inform a tailored framework ~~for stakeholder engag~~ement processes in future ~~early~~ economic evaluation ~~studies~~ model development.'

The following has been updated in the introduction (new text is underlined):

Traditionally, stakeholder engagement in economic evaluations has focused on consulting industry representatives, policy makers, and reimbursement decision-makers to define research questions and confirm model parameters. These stakeholder groups represent the key knowledge users of the outputs of health economic evaluations. Whereas these professional groups are dominant in the use of health economic evaluation results, other stakeholders, such as patients and their caregivers, are directly affected by the resulting decision making of these groups~~; however~~. Involving other stakeholders, such as clinicians, patients, and their support networks ~~during the conduct of~~ in the development of HE evaluation models can provide additional insight into a model structure, ~~factors~~, input parameters and assumptions, that may enhance the validity and generalizability of an economic model.

Stakeholder engagement in the broader field of health technology assessment, with which economic evaluation is a part, is not novel and represents an area of work that has received significant focus in health technology assessment literature and practice alike.

Thank you for highlighting the environmental science literature as it relates to stakeholder engagement in economic model development. We've referenced some of the existing literature in this field in our

manuscript; however, we recognise that there is value in elaborating this reference to compare and contrast the implications of this work on our own in health economic model development. As such, we've added the following text (new text is underlined)

… however, evidence from other fields (e.g., environmental sciences and conservation) demonstrates the importance of involving key stakeholders in good modelling practice,[13-22] including the incorporation of stakeholder perceptions of model salience and legitimacy.[13] Parallels exist between environmental and HE modelling in that these models bridge the science-policy gap and support decision-making. The benefits reaped in the field of environmental modelling from stakeholder engagement, such as increasing model validity, advancing methods in the co-production of knowledge, and contributing to shared decision-making, facilitating easier and improved decisions, represent untapped potential in HE modelling; however, the relevant stakeholders in HE modelling may include specific, and potentially very small subsets of the population, and with a dearth of evidence, it is unclear whether these benefits will translate to this field of modelling.

2. Definition of early Health Economic Model. It was not clear why the objective is to develop an early or iterative model (not necessarily the same). It would be helpful to define more carefully what decision the early model is expected to inform. If it is iterative, ie is the expectation to inform decisions along the development of the model or with more evidence becoming available?

Thank you for drawing our attention to this ambiguity in the manuscript. We've updated the manuscript to more clearly define the objective of the economic model development; namely, with the study of CAR-T therapy for use in this specific patient population in its infancy, the objective of the project is to develop an early health economic evaluation model given the lack of evidence at this stage of research and development, and the model will be updated iteratively as new evidence emerges. As early economic evaluation is recognized as a tool to support product investment decision-making, the rationale for the early health economic evaluation model development is to identify particular patient and intervention characteristics that will make CAR-T therapy reimbursable. We've clarified this point with the inclusion of the following text:

An early economic evaluation can support product investment decision-making, which is pertinent to CAR-T therapy, as it exists in a complex intellectual property landscape and funding for clinical trial support in Canada is likely to rely on non-commercial resources. The application of this model will help identify particular patient and intervention characteristics that will make CAR-T therapy reimbursable.

3. Exploring experiences in public policy I had the privilege to work with public policy scientists on a few papers and there is some interesting literature in that space you may need to refer to. This is not only limited to stakeholders perspectives on developing the models, but also about stakeholders perspectives relevant to make an impact in policy.

Thank you for this comment and for highlighting this pertinent literature. It is helpful to reference the broader literature surrounding health policy, and how the early assessment of medical technologies can inform both product development and market access. We've referenced this literature to better situate the current project along the continuum of health technology development, and more clearly articulated the intent of the present early health economic evaluation model development and the resulting implications

*for the nature and roles of stakeholders given the stage of development of CAR-T therapy for the specific patient population being investigated. The following text has been added to the manuscript, including the associated reference, 'Ijzerman MJ, Steuten LM. Early assessment of medical technologies to inform product development and market access: a review of methods and applications. Appl Health Econ Health Policy 2011 Sep 1;**9**(5):331-47. doi: 10.2165/11593380-000000000-00000. PMID: 21875163.':*

Resultantly, early health economic evaluations, a central component of early health technology assessments, have applications to inform decisions made by health policy makers and industries. In the case of health policy, early assessments provide insight into the potential impact of emerging technologies to inform future policy and market access, whereas industry gains from insight used to inform product research and development decision-making.

4. Defining stakeholders and decision makers Most of the models we develop in HTA have a rather limited scope compared to some of the environmental models you refer to in the literature. The decision is relevant for a (very) small group of patients and the decision makers involved are relatively limited.

Potentially, there is a much larger group of stakeholders either directly or indirectly using the evidence presented in the models. For instance, neither industry reps nor politicians are included. I can see why not, but they can be dominant and clearly play a role in use of economic evaluation results. I'd recommend to carefully define stakeholder groups, to define their potential role and dominance in the use of economic evaluation results.

Thank you for drawing attention to this point. We engaged in several discussions pertaining to the relevant stakeholders to engage in the development of this early health economic evaluation model. While decisions regarding the reimbursement model for the specifically referenced therapy will directly affect a small group of patients, the wider implications of the allocation of healthcare dollars will have extended, indirect effects for a much larger group of stakeholders, as you mention. We felt that it was important to focus on specific stakeholder groups who have not traditionally been given the platform to provide their input in economic analysis, such as patients, and that that at an early stage, input from this group would be the most pertinent. We recognize that other stakeholder groups, such as the general public, industry, and politicians would need to be included for the implementation of the health economic model results, but this was outside the scope of the current study and was thought to be of greater importance at a later stage. We acknowledge this limitation in the manuscript with the following text (new text is underlined), 'however, additional stakeholders, such as the general public, industry, and politicians would need to be included for the implementation of the HE model results and is outside the scope of the present study.'

We have included additional text in the manuscript to outline and define the relevant stakeholder groups in this early health economic evaluation (new text is underlined):

Traditionally, stakeholder engagement in economic evaluations has focused on consulting industry representatives, policy makers, and reimbursement decision-makers to define research questions and confirm model parameters. These stakeholder groups represent the key knowledge users of the outputs of health economic evaluations. Whereas these professional groups are dominant in the use of health economic evaluation results, other stakeholders, such as patients and their caregivers, are directly affected by the resulting

decision making of these groups~~; however~~. Involving other stakeholders, such as clinicians, patients, and their support networks ~~during the conduct of~~ in the development of HE evaluation models can provide additional insight into a model structure, ~~factors~~, input parameters and assumptions, that may enhance the validity and generalizability of an economic model.

5. Alignment with guidelines

Many of the health economic models are developed based on modelling guidelines issued by HTA agencies. These guidelines prescribe what evidence needs to be demonstrated and what the base case should be. Can the authors please indicate how much opportunity there is to deviate from these guidelines by consulting with stakeholders? Or, alternatively, how can we ensure that stakeholder perspectives are given a weight in the model development by users of these models.

Thank you for your insightful comments. We agree with the reviewers that most health economic evaluations (and models) are driven by economic evaluation guidelines, which indicate a preferred "reference case". These guidelines, however, provide broad recommendations on the model development process. CADTH economic evaluation guidelines, for example, suggest that:

"…The conceptualization of the model should incorporate the potential for changes along the clinical or care pathway...The model structure must be clinically relevant, and close collaboration with and input from those able to provide clinical expert judgment is necessary. The model must be consistent with the current knowledge of the biology of the health condition, the causal relationships among variables that constitute the clinical or care pathway, and the expected effects of the interventions…"

A wide scope of recommendations offers the opportunity to use our proposed framework to meaningfully engage relevant stakeholders to enhance the validity of the model.

6. Methods used

I have insufficient experience with the NGT methods used, but there are similarities with MCDA methods. Three questions with regard to the proposed methods, (1) why define separate stakeholder groups and why don't you bring them together to discuss different perspectives (see decision conferencing methods), (2) the exploration and structuring phase can all be brought into one session, is this considered? and (3) you refer to ranking but no methods are defined. How obtained and are these ranks used to facilitate the group discussion?

Thank you for highlighting the similarities between MCDA and the Nominal Group Technique approach that we applied for this project. Indeed, there are several similarities. While there are similarities, we

chose to use the NGT for this project because rather than arrive at a decision based on pre-determined criteria, this project sought to identify several different stakeholder-identified criteria/inputs that should be included in health economic evaluation models, such as the early health economic evaluation model of CAR T-cell therapy we are developing. In essence, this project falls into the 'Selecting and Structuring Criteria' step in conducting an MCDA. We have included a response to each of your specified questions below.

1. *Separate stakeholder group discussions were held to limit the influence of power dynamics on the outputs generated in the group discussions. The research team strived to eliminate power imbalances between the research team and discussion participants, and between participants*

themselves, through the specific methods chosen (reducing power imbalances is a key strength of the NGT) and in consultation with our patient and knowledge user partners. We believe that in conducting discussions separately with each stakeholder group, participants would feel more comfortable sharing their thoughts and ideas. This is particularly important for the patient and caregivers' stakeholder group discussions, as placing a monetary value on a potentially life-saving therapy may lend itself to emotionally charged discussions. Moreover, the specific points addressed by each stakeholder group are different; patients are engaged to provide their input on the costs and benefits that should be considered in the model; clinicians and researchers are engaged to provide their insight into the specific sequences of therapy that should be reflected in the model, and; policymakers and healthcare decision-makers are engaged to provide their insight into the specific outputs of health economic evaluation models that would be the most valuable to enhance their uptake in healthcare decision-making. The research team is comprised of representatives from each of these stakeholder groups, and through regular project meetings over the course of data collection and afterwards, we will triangulate the different perspectives raised by each of the stakeholder groups.

2. *Using the NGT, one session will be held with each stakeholder group where participants will generate ideas in response to the specific questions posed, which will generate inputs that will inform the economic evaluation model. The questions are designed to elicit reflection on the important considerations, including model inputs and outputs, that should be taken into account in the development of the HE evaluation model of CAR-T therapy to ensure stakeholders' experience and expertise are represented. During the same session, participants will discuss the ideas generated, clarify these where needed, and group similar ideas under corresponding themes. Participants will then independently rank the themes and ideas that were generated in the group discussion using an online feedback form. The ranking was transitioned to online asynchronous methods given the independent nature of this task and to optimise the online group discussion; feedback from patient partners highlighted the importance of group discussions that were concise and not too long to optimise participants' contributions. In this same vein, the results discussion was transitioned to online asynchronous communication via email, allowing for participants to engage at their convenience.*

3. *Participants will rank the ideas generated during the group discussion using an online feedback form that will be populated based on the discuss outputs and shared with participants following the stakeholder group discussion. The rankings will not be used to facilitate the online group discussion, but rather will be shared for asynchronous comment via email for those participants who express interest in receiving this list.*

The following text has been added to the manuscript to clarify this point (new text is underlined): 'Participants are asked to individually rank all of the proposed additional inputs, outputs, and model adjustments <u>following the discussion using an online feedback form</u>', and 'Participants will then be asked to individually rank the <u>groupings that were generated in the discussion, as well as the individual</u> propose<u>d</u> additional inputs, outputs, and model adjustments using the <u>feedback form.</u>' Additionally, we

have added the following text to indicate how the rankings contribute to a results discussion (new text is underlined): 'Results discussion: Participants are invited to provide their comments and thoughts on the final ranked list once everyone has completed the online ranking exercise via email' and 'Following completion of the feedback form, the results of the participants' rankings will be tallied and shared with participants who indicate their interest for asynchronous comment via email to provide insight into the intricacies underlying the ranked list.' We recognize the value of using the rankings to contribute to the synchronous group discussions; however, as a result of the pandemic and the adaptation of the

Nominal Group Technique for an online platform, this component was transitioned to being held online using asynchronous methods.

Reviewer: 1

Competing interests of Reviewer: None declared

Reviewer: 2

Competing interests of Reviewer: None

Reviewer: 3

Competing interests of Reviewer: None declared.

VERSION 2 – REVIEW

REVIEWER	Ijzerman, Maarten University of Twente
REVIEW RETURNED	02-Apr-2021

GENERAL COMMENTS	Thank you for the detailed response to the questions and for addressing all comments made. I am satisfied with the changes made in the manuscript. One minor comment is the reference to our work in the revised manuscript. I actually wasn't intending you to cite our paper, but to other literature that may be known as pre-assessment. There is some international work on usefulness of modelling to inform HTA decisions. One example is: an Gool K, Gallego G, Haas M, Viney R, Hall J, Ward R. Economic evidence at the local level : options for making it more useful. Pharmacoeconomics. 2007;25(12):1055-62.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Maarten Ijzerman, University of Twente

Comments to the Author:

Thank you for the detailed response to the questions and for addressing all comments made. I am satisfied with the changes made in the manuscript.

One minor comment is the reference to our work in the revised manuscript. I actually wasn't intending you to cite our paper, but to other literature that may be known as pre-assessment. There is some international work on usefulness of modelling to inform HTA decisions. One example is: an Gool K, Gallego G, Haas M, Viney R, Hall J, Ward R. Economic evidence at the local level : options for making it more useful. Pharmacoeconomics. 2007;25(12):1055-62.

Reviewer: 3

Competing interests of Reviewer: No

Thank you for clarifying your previous comment and for identifying this literature. Though the focus of the protocol is on economic model development, we have elaborated on the use of economic models, and indeed the barriers and facilitators to doing so, in the discussion with reference the literature suggested. The following text has been added to the manuscript with the appropriate references:

'Moreover, research aimed to bridge the evidence-to-policy gap suggests that involving knowledge users (i.e., healthcare payers and policy makers) throughout the model development process will ensure their information needs are met and enable economic evaluation models to effectively contribute to healthcare decision-making.[66,67,68]'

*66. van Gool K, Gallego G, Haas M, Viney R, Hall J, Ward R. Economic evidence at the local level : options for making it more useful. Pharmacoeconomics. 2007;**25**(12):1055-1062. doi:10.2165/00019053-200725120-00006*

*67. Borowski HZ, Brehaut J, Hailey D. Linking evidence from health technology assessments to policy and decision making: the Alberta model. Int J Technol Assess Health Care. 2007;**23**(2):155-161. doi:10.1017/S0266462307070250.*

*68. IJzerman MJ, Reuzel RP, Severens HL. Pre-assessment to assess the match between cost-effectiveness results and decision makers' information needs: an illustration using two cases in rehabilitation medicine in The Netherlands. Int J Technol Assess Health Care. 2003;**19**(1):17-27.*